

REMARKS

Claims 2, 19 and 40 have been canceled herein. Claims 1, 3-18, 20-39 and 41-60 are pending in the application.

Claim Rejections-35 USC §103

The Examiner has rejected claims 1-60 under 35 USC §103(a) as being unpatentable over Edwards (5,985,309) in view of Patton (5,997,848). The Examiner states (page 4, Office Action) that it would have been obvious to a person skilled in the art to have modified the formulations of Edwards containing insulin, DPPC and excipients such as lactose with the insulin formulations as taught by Patton and to have substituted the lactose with sodium citrate since Patton discloses that lactose and sodium citrate are equivalent carriers. Please note that not only do the references not teach the specific combination of components, the references do not teach the specific amounts of the components in the claimed formulations.

Applicants respectfully disagree with the Examiner's conclusion. Patton does not state anywhere that lactose and sodium citrate are "equivalent" carriers. Chemically, the two are very different from one another. Patton's disclosure of lactose and sodium citrate as members of a Markush group also does not establish the equivalency of these components (*In re Ruff*, 256 F.2d. 590, 118 USPQ 340 (CCPA 1958)).

The Examiner attempts to establish that the equivalency of sodium citrate and lactose is recognized in the prior art by stating (page 5, Office Action) that sodium citrate has a dual buffering and carrier function and therefore, one skilled in the art would be motivated to select sodium citrate over lactose. While Applicants do not dispute that sodium citrate is generally understood to be a buffer for numerous uses and not just in the production of insulin dry powders, Applicants disagree with the Examiner's conclusion that this property would lead one skilled in the art to select sodium citrate over lactose in the formulations disclosed by Edwards. For example, Edwards clearly does not suggest or disclose that sodium citrate is interchangeable with lactose. In contrast to the relatively large list of carriers and excipients recited by Patton, Edwards' list of excipients is short and very specific and includes only a sugar, such as lactose, a protein, such as albumin and/or a surfactant, such as DPPC.

Therefore, Applicants submit that there is no motivation in any of the cited references or in the general prior art to replace sodium citrate disclosed by Patton with lactose disclosed in Edwards. The Examiner is resorting to hindsight reconstruction to conclude that the presently claimed invention is obvious in view of the cited combination of references, and this is impermissible. Applicants submit that the Examiner has not established a *prima facie* case of obviousness in view of the cited combination of references.

In further support of the patentability of the presently claimed invention, Applicants are submitting a declaration under 37 C.F.R. §1.132. The declaration establishes that not only can the selection of the excipients result in substantial differences in the product, but also the amounts of the excipients selected. In the declaration, Declarant shows that formulations that differ solely in the relevant amounts of the hydrophobic component (e.g., DPPC), citrate and insulin can have substantial differences in manufacturability. Specifically, increasing the amount of insulin in the formulation from 10% to 30%, with a corresponding decrease in the lipid (i.e. "hydrophobic") component, DPPC, dramatically and unexpectedly improved the solubility of the total solids in the spray drying solution.

Applying this showing to the example of Edwards, the closest working examples of Edwards had only about 2% by weight human insulin. See Example 9, for example. The solids content of the spray dry solution was only 0.1 % w/v. Edwards provides little guidance as to how one would achieve a large scale process by increasing the solids content of the spray drying solution. Further, Edwards does not teach how one would do so with a formulation containing a higher concentration of insulin. Based on the disclosure of Edwards, the enclosed formulation for providing a good to excellent load of insulin, and corresponding pharmacokinetic profile, with good to excellent manufacturability would not have been obvious.

With respect to the provisional rejection under the doctrine of obviousness-type double patenting, Applicants submit that, since the claims have been amended to avoid any overlap in subject matter, the rejection is deemed moot.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If

the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

ELMORE CRAIG, P.C.

For: Carolyn S. Elmore 35,729
By Carolyn S. Elmore
Carolyn S. Elmore, Esq.
Registration No. 37,567
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

Dated: April 20, 2004